Malvern

SCOPING THE DESIGN SPACE FOR GENERIC NASAL SPRAYS

In this article, Deborah Huck-Jones, PhD, Product Manager, Analytical Imaging; and Paul Kippax, PhD, Micrometrics Product Group Manager & Pharmaceutical Portfolio Manager, both of Malvern Instruments, discuss analytical methods that can be helpful for demonstrating bioequivalence in the development of generic nasal sprays, highlighting the importance of understanding how spray formulations and devices interact to impact drug delivery performance.

As a result of the regulatory focus on using a Quality by Design (QbD) approach for ANDAs, generics manufacturers are placing increasing emphasis on the analytical tools that support its application. Most especially, there is a requirement for analytical technologies that help to scope the product design space efficiently. This is the multi-parametric space in which the properties that define clinical performance must lie to ensure consistent, controlled efficacy.

When developing nasal sprays, identifying the design space is complicated by the fact that critical features of the delivered dose, such as droplet size, are influenced by interactions between the formulation and the delivery device used. A detailed understanding of the impact of both of these elements is essential to achieving the QbD, knowledge-led approach now associated with successful development and commercialisation of a generic.

Here, we examine the complementary use of laser diffraction particle sizing, automated imaging and rheological characterisation to gather the information needed both for generic nasal spray development and the demonstration of bioequivalence. In combination these techniques help to elucidate the factors defining product performance. This enables efficient manipulation of the formulation properties and the features of the device in order to meet development targets.

THE REGULATORY FRAMEWORK

In recent years, the US FDA's Office of Generic Drugs (OGD) has strongly encouraged the adoption of QbD in the development of generic drugs and, as of January 2013, all ANDAs are expected to follow this risk-based, scientifically rigorous approach. QbD includes the setting of a quality target product profile (QTPP) for the drug product, a specification that defines clinical performance, and identification of the critical quality attributes (CQAs) that deliver it.

The focus of generic product development is to replicate the exact pharmacological behaviour and bioavailability (BA) of an innovator drug, to demonstrate bioequivalence (BE) between the two products. Setting of a QTPP is therefore relatively straightforward. Identifying CQAs for the product, and learning how to manipulate them to meet performance targets, forms the bulk of the de-formulation process in the application of QbD for generic development.

Because of a global increase in respiratory disorders - particularly within recently industrialised regions[1] - OINDPs are an important target for generic development and manufacture. However, duplicating OINDP performance presents unique challenges since both the device and formulation require knowledgeable management to ensure complete emulation of the innovator.

Focusing on nasal sprays, the FDA guidance for characterising the BE of locally-acting drugs delivered by nasal sprays forms a useful basis for QbD studies.[2] This guidance includes a number of *in vitro* tests, placing the emphasis on attaining a comprehensive understanding of API particle and spray droplet size, and the way in which these change throughout the drug delivery process. Laser diffraction is the recommended technique for determining droplet size distribution while microscopy is highlighted for studies of the active ingredient within a suspension formulation.

Dr Deborah Huck-Jones
Product Manager,
Analytical Imaging.

Dr Paul Kippax
Micrometrics Product Group Manager & Pharmaceutical Portfolio Manager
T: +44 1684 892456
F: +44 1684 892789
E: paul.kippax@malvern.com

Malvern Instruments Ltd
Enigma Business Park
Grovewood Road
Malvern
Worcestershire
WR14 1XZ
United Kingdom

www.malvern.com

MECHANISMS OF NASAL SPRAYS

Nasal spray formulations usually consist of an API that is dissolved or suspended in an aqueous solution. Controlling the size of the delivered droplets is crucial to successful *in vivo* drug deposition. Typically, nasal sprays destined for deposition in the naso-pharyngeal region – such as common cold and influenza remedies – will be designed to deliver a droplet size of 20-120 µm. Particles below the lower limit are susceptible to inhalation into the lungs while those that are too large tend to remain in the front of the nose or are lost through dripping. Droplet size is therefore a CQA – a performance-defining parameter – for nasal sprays.

The droplet size delivered by a nasal spray is a function of the physical properties of a formulation, most notably its viscosity, and also the mechanism and geometry of the nasal spray pump. Key characteristics of the pump include the applied actuation profile, the pump pre-compression ratio and the length, geometry and orifice size of the actuator. Together, these determine the shear-force applied to the formulation during actuation and, as a result, the size of the droplets delivered.

By manipulating device and formulation variables, product developers tune nasal spray systems to deliver the required droplet size. Therefore, both the parameters of the pump and the physical properties of the formulation, such as viscosity, are critical material attributes (CMAs), variables that have a direct impact on the CQA droplet size, which must be controlled to ensure the BE of a generic nasal spray.

Suspension nasal sprays bring a further level of complexity, as both the size of the droplets produced by the nasal spray and the size of the suspended API must be considered. The API particles are potentially vulnerable to changes in morphology during the actuation process. Such changes may, in turn, affect bioavailability. The API particle size is therefore another CMA which must be considered as part of the demonstration of BE, with the FDA's guidance suggesting measurements pre- and post-actuation.

In summary, the de-formulation of both solution- and suspension-based nasal spray products relies on understanding the dynamics of atomisation and how to control CMAs to meet droplet-size targets. For suspension-based products there is an additional requirement to assess the impact of actuation on the delivered API particle size. In combination these requirements for particle/droplet size analysis constitute the majority, and the most demanding, element of BE testing.

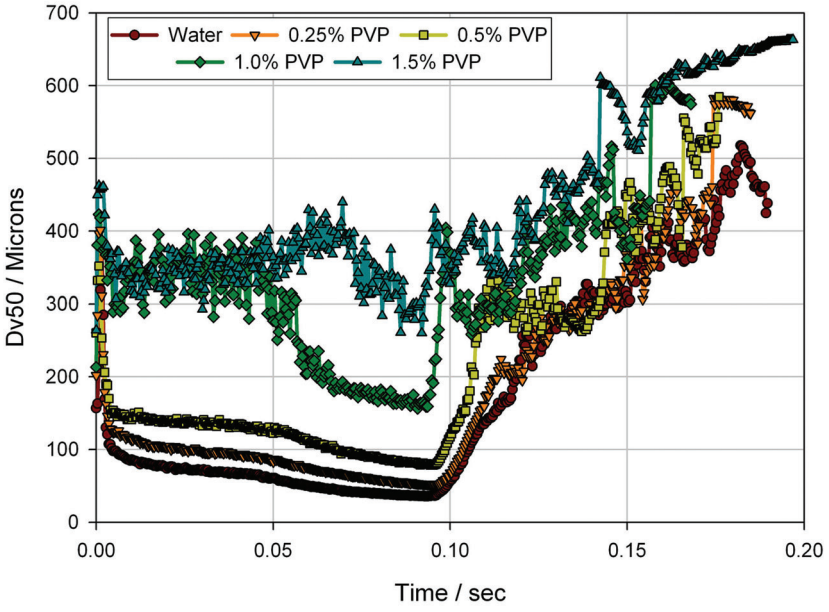


Figure 1: The evolution of droplet size (Dv50) during delivery via a nasal spray for solutions of PVP in water.

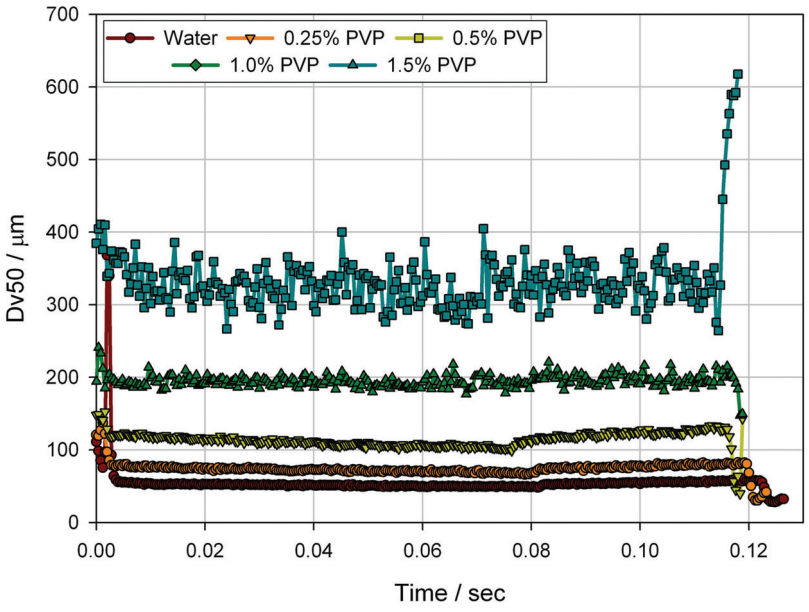


Figure 2: The evolution of droplet size (Dv50) during delivery using an alternative nasal spray pump for solutions of PVP in water.

THE NASAL SPRAY DE-FORMULATION TOOLKIT

FDA guidance recommending the use of laser diffraction for droplet size measurement makes this technique central to the nasal spray de-formulation toolkit. The following case studies show how laser diffraction and automated image analysis work in tandem to elucidate the performance of nasal spray products and support de-formulation studies.

Case study 1: Laser Diffraction to Investigate Impact of Formulation Viscosity

Laser diffraction systems determine droplet size and size distributions by measuring the angular variation in the intensity of light scattered by droplets as a laser passes through a spray. Rapid data acquisition, coupled with the ability to measure size distributions over a wide range (0.1-2000 µm), makes laser diffraction an ideal tool for studying atomisation dynamics. Measuring droplet size distributions in real time during nasal spray actuation can help formulators quantify how variations in CMAs, such as formulation viscosity or nozzle geometry, impact droplet size.

Figure 1 illustrates how laser diffraction measurements can be used to investigate the impact of changes in formulation viscosity on atomisation behaviour and delivered

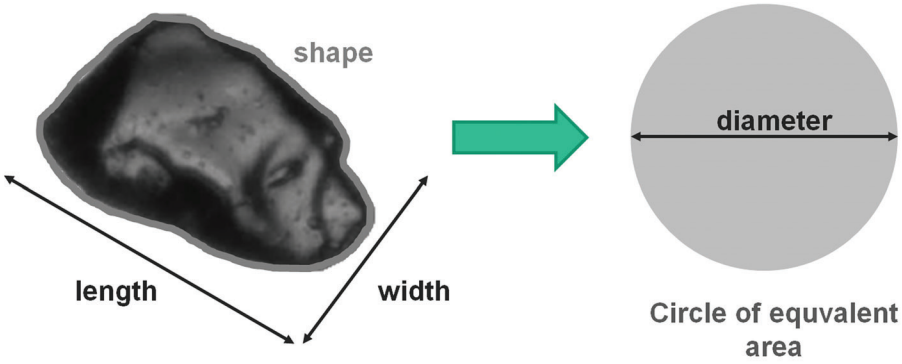


Figure 3: Automated morphological imaging captures individual 2D particle images and uses them to determine size/shape distributions. Conversion to a circle of equivalent area enables a spherical equivalent diameter to be calculated.

droplet size for a nasal spray. In these tests four polyvinylpyrrolidone (PVP) solutions of different concentrations and one water sample were atomised using a commercially-available nasal pump. Actuation was carried out using a fixed actuation velocity and the evolution of droplet size was tracked, from actuation through to completion of the spray event, using a Spraytec laser diffraction particle size analyser (Malvern Instruments, UK). The entire spray event lasts only 160 ms, emphasising the need for rapid data capture.

For the three lower-viscosity solutions, three discrete phases – formation, fully formed/stable dispersion and dissipation – are observed, as defined in the FDA's BA/BE guidance.[2] During the formation phase the droplet size decreases sharply as the pump becomes primed and the flow rate of the liquid formulation through the device increases. During the stable phase a steady flow rate is established through the pump nozzle and the bulk of the dose is delivered at a consistent droplet size. However, as the device begins to empty, flow through the nozzle decreases once again leading to a larger droplet size in the dissipation phase.

At higher viscosities, for the 1.0 and 1.5 % w/w PVP solutions, the actuation process is clearly less successful. Droplet size is not only much larger, but it is also unstable and the fully developed phase is less well defined. The inference from this experiment is that the formulation must have a viscosity that is equal to or below that of the 0.5 % w/w PVP solution if successful delivery with this device is to be ensured.

In this example, viscosity measurements in combination with laser diffraction particle sizing enable the determination of a desirable range of viscosity. This is an important step in scoping the design space for the product.

Case study 2: Laser Diffraction to Investigate Impact of Pump Mechanism

When the same PVP solutions are atomised using a nasal spray pump with an alternative operating mechanism, the results obtained can be quite different. Figure 2 shows how a second pump design produces a long and stable phase for every solution, even those that have a high formulation viscosity, suggesting more consistent, reproducible delivery. This clearly illustrates how the pump design can have a marked impact on the success, or otherwise, of drug delivery.

The nasal pump that generated the results shown in Figure 2 employs an energy storage unit which releases only when the pump reaches a pre-determined hydraulic pressure. However, even with this more sophisticated device, delivered droplet size remains a function of viscosity. At high viscosities the shear applied by the pump is still insufficient to fully atomise the formulation in order to yield the fine droplets produced at lower viscosities. These droplet sizing results, as with those in the preceding case study, allow the definition of a desirable range for viscosity, one that delivers consistent dispersion to the target droplet size, with the specific device.

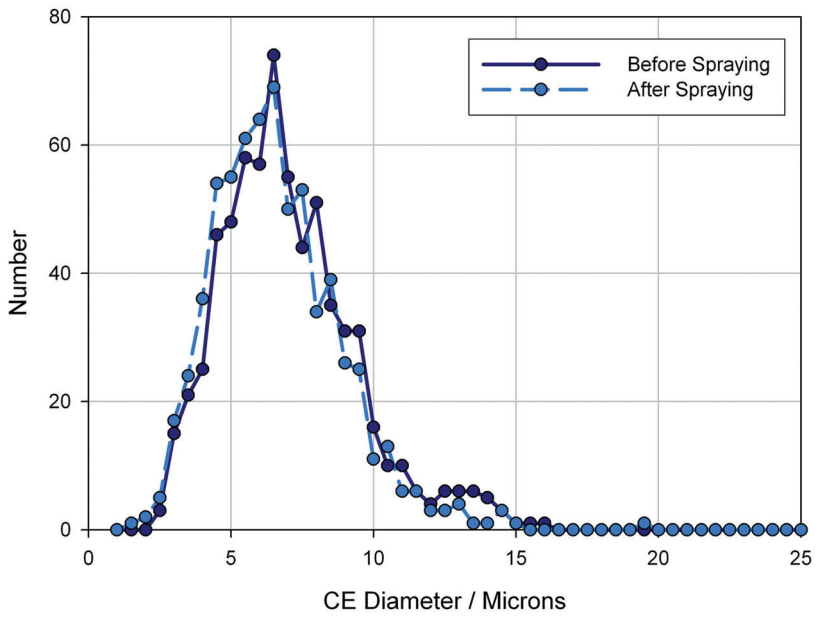


Figure 4: The API within a nasal spray suspension shifts slightly to the left following actuation, suggesting particle dispersion.

Case study 3: Automated Morphological Imaging for API Particle Sizing

Both of the first two case studies described demonstrate the utility of laser diffraction in de-formulation research. They highlight the technique's ability explore the physical aspects of the formulation and the device, producing information that helps formulators to achieve the target droplet size for nasal spray solutions. However, laser diffraction makes measurements on the formulation as a whole. It does not provide component-specific measurements of the API suspended within a droplet. For suspension nasal sprays, supplementary analysis is required to differentiate the API from other suspended solids and to quantify the impact of the spray process on API morphology.

The requirement set out in the FDA BE guidance, to measure the particle size of the API pre- and post-actuation, can be met using manual microscopy. Automated imaging is an alternative approach that offers substantial benefits, not least because automation removes subjectivity from the analysis and significantly reduces operator input. Automated imaging involves capturing individual two-dimensional images of dispersed particles and building size and shape distributions from the dimensions of each image (Figure 3).

Figure 4 shows particle size distribution data for an API dispersion within a nasal spray suspension, before and after actuation,

gathered using an automated morphological imaging system (Morphologi G3, Malvern Instruments). In this formulation the excipients and API had distinctly different morphology, so classification based on size and shape alone was sufficient to identify the API population, and produce component-specific particle size distribution data. The particle size distribution profiles shown in Figure 4 indicate that actuation produces a slight shift in API particle size towards finer sizes, suggesting particle dispersion during the atomisation process. Such an effect may impact the bioavailability of the API and its uptake *in vivo*, potentially influencing clinical efficacy.

In the preceding example, API and excipient were differentiated on the basis of shape alone. In many suspensions this is not possible, and this is where the additional capability of Raman spectroscopy – chemical identification – becomes valuable in enabling successful de-formulation. Morphologically directed Raman spectroscopy (MDRS), as applied in the Morphologi G3-ID (Malvern Instruments), involves gathering spectra from targeted particles, identified on the basis of size and shape. These spectra are then compared with a set of reference spectra to determine the chemical nature of the individual particles. Particles with a high correlation with a specific reference spectrum, as assessed using a least-squares fit correlation factor, can be positively identified. If features from multiple reference spectra are identified then this may indicate that a particle is an agglomerate.

Figure 5 shows Raman spectral correlation scores for particles in a nasal spray formulation containing morphologically similar components. The scatter plots show two distinct particle populations, one cluster with a high correlation score relative to an API reference spectrum and another with a high correlation compared with an excipient reference spectrum.

Images of particles identified as API show that they are relatively spherical compared with the more elongated excipient particles. Figure 6 shows shape distribution data for the two-component populations. These data suggest that particles with an elongation ratio of 0.5 or higher can be allocated to the excipient population. However, there are an appreciable number of particles that, on the basis of the shape, could be either API or excipient. Targeting Raman spectroscopy on particles with these properties ensures accurate particle size determination while at the same time minimising the longer measurement times associated with the application of standard Raman mapping.

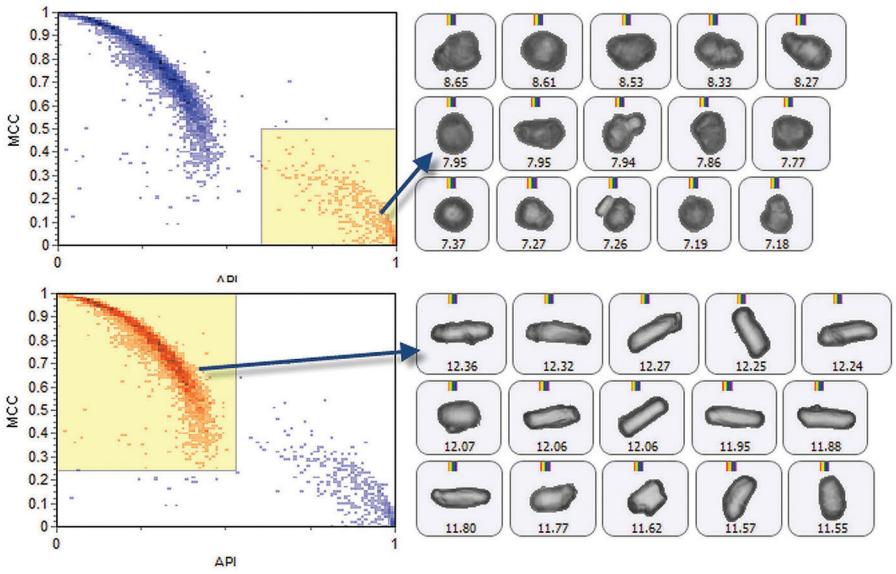


Figure 5: Scatter plots for Raman correlation scores of API and excipient particles quantify the relative amounts of each constituent, overcoming morphological similarity.

LOOKING FORWARD

OINDPs present a unique challenge to developers of generic pharmaceuticals because achieving bioequivalence relies on knowledgeable manipulation of the physical properties of the formulation as well as the characteristics of the device. Techniques such as laser diffraction and MDRS have an important place in the de-formulation toolkit. In combination with rheological characterisation, most especially viscosity measurement, these tools help with fast and efficient QbD ANDA submissions.

The authors would like to acknowledge the kind support of Next Breath in helping to define and carrying out the measurements described.

REFERENCES

1. *Khaled N et al, "Chronic respiratory diseases in developing countries: the burden and strategies for prevention and management". WHO Bulletin, 2001, 79.*
2. *"Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action", US FDA CDER Biopharmaceutics, April 2003.*

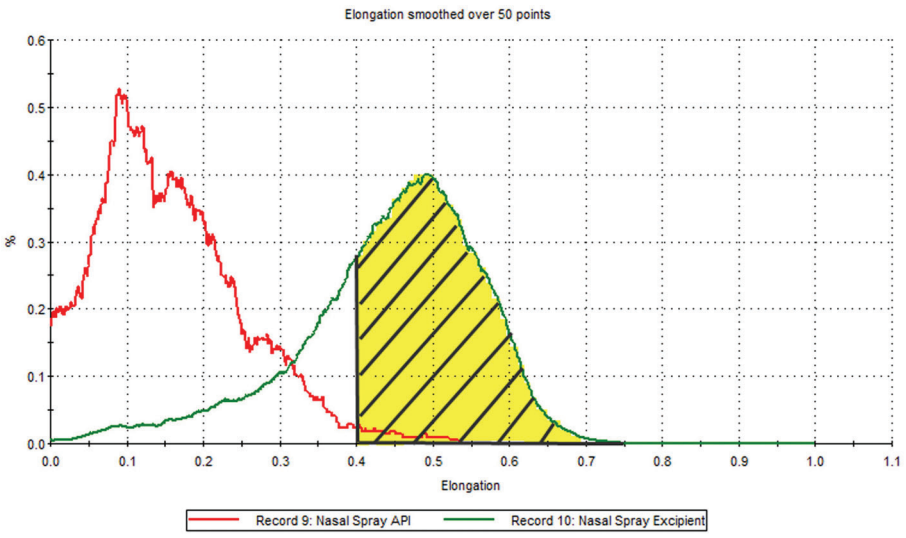


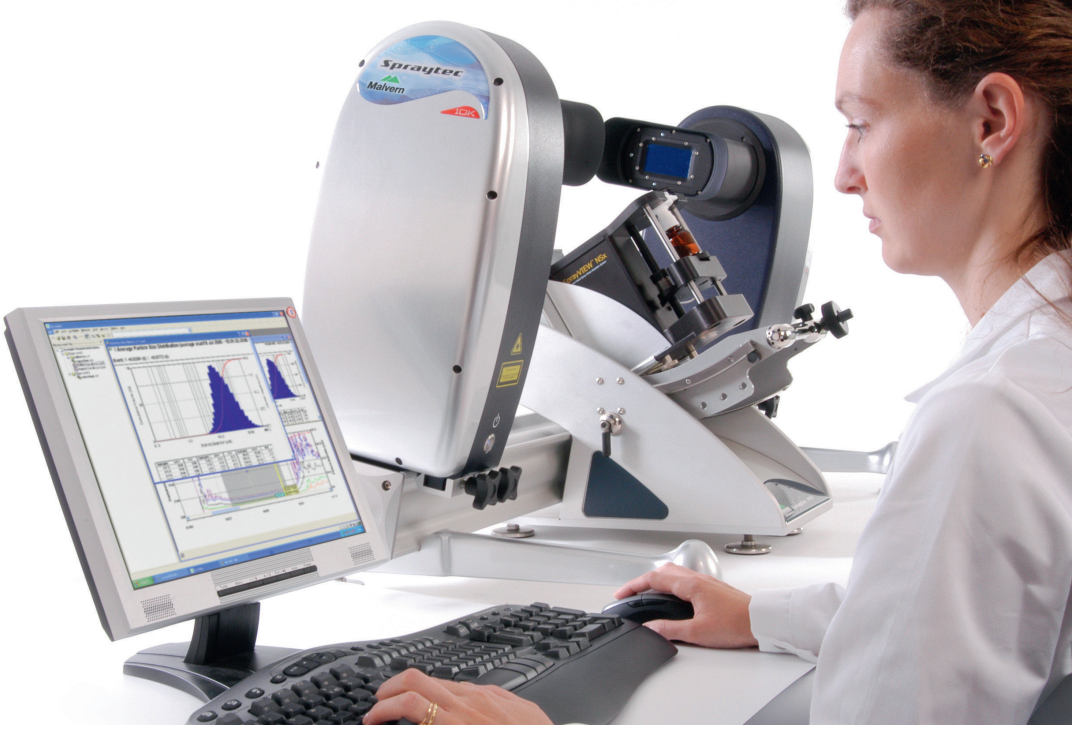
Figure 6: Shape distribution data for excipient and active ingredients within a formulation successfully identified using morphologically-directed Raman spectroscopy. The region shaded within the excipient distribution was not target for Raman analysis as particles in this region could be identified by size and shape alone.

FROM **SPRAYS...**

SPRAYTEC:
Dynamic particle and droplet sizing

- Measures concentration and particle/ droplet size during device actuation
- Rapid screening and accelerated optimization of OINDP formulations and delivery device
- Complementary to other analysis methods such as cascade impaction
- Promotes a knowledge-based approach to product development advocated by QbD

www.malvern.com/spraytec



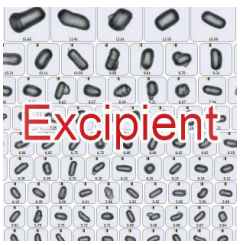
CHARACTERIZE YOUR OINDP IN **DETAIL**

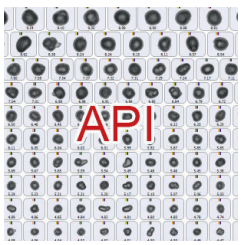
www.malvern.com/g3id

...TO **API SIZE**

MORPHOLOGI G3-ID
Morphologically Directed Raman Spectroscopy

- Component specific particle size and shape distribution measurements for OINDP formulations
- Simple SOP operation from sample dispersion through to size, shape and chemical analysis
- Provides supporting evidence for in-vitro bioequivalence and CMC studies for nasal sprays
- Aids the deformulation of OINDP formulations, promoting a QbD focused approach to ANDA submissions





Malvern | Material relationships

www.malvern.com